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Molecular genetics of the swine major histocompatibility complex, the SLA complex

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ABSTRACT

The swine major histocompatibility complex (MHC) or swine leukocyte antigen (SLA) complex is one of the most gene-dense regions in the swine genome. It consists of three major gene clusters, the SLA class I, class III and class II regions, that span ~1.1, 0.7 and 0.5 Mb, respectively, making the swine MHC the smallest among mammalian MHC so far examined and the only one known to span the centromere. This review summarizes recent updates to the Immuno Polymorphism Database-MHC (IPD-MHC) website (http://www.ebi.ac.uk/ipd/mhc/sla/) which serves as the repository for maintaining a list of all SLA recognized genes and their allelic sequences. It reviews the expression of SLA proteins on cell subsets and their role in antigen presentation and regulating immune responses. It concludes by discussing the role of SLA genes in swine models of transplantation, xenotransplantation, cancer and allergy and in swine production traits and responses to infectious disease and vaccines.

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1. Overview

Advances in genomics have deepened our understanding of how the immune system is regulated and identified genes that influence these processes. Yet the genes that are most important for the immune response to swine infectious diseases and vaccines are still those of the swine major histocompatibility complex (MHC), the swine leukocyte antigens (SLA). This review will summarize the current knowledge of the genomics of the SLA region, dissect the polymorphisms of each locus and discuss the methods now used to more effectively identify these alleles. This review will end with studies of SLA gene regulation of swine disease responses, including recent data on PRRS resistance, and the importance of whole genome mapping efforts in determining disease and vaccine responses.

2. SLA complex genome map

2.1. Organization of the SLA complex

The SLA complex is one of the most gene-dense regions in the swine genome. It consists of three major gene clusters (class I, III and II) and has been mapped to chromosome 7 spanning the centromere [1,2]. The class I and class III regions are located in the 7p1.1 band of the short arm (Fig. 1) and the class II region is located in the 7q1.1 band of the long arm (Fig. 2) [3]. This physical assignment of the swine MHC spanning the centromere of SSC7 is unique among mammals studied to date [3]. Sequencing and mapping of the entire SLA region of the very common Hp-1.1 (H01) haplotype has been completed [4–9]. The SLA class I, class III and class II regions were found to span approximately 1.1, 0.7 and 0.5 Mb, respectively, making the swine MHC the smallest among mammalian MHC so far examined. Over 150 loci have been identified in the entire SLA region and at least 121 genes are predicted to be functional [4–9]. This review builds on previous reviews of the SLA complex [10–15].

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Abbreviations: ASFV, African swine fever virus; APC, antigen presenting cells; b2m, β_2-microglobulin; CSFV, classical swine fever virus; CYP21, cytochrome P450 21-hydroxylase; DC, dendritic cells; FMDV, foot-and-mouth disease virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IPD-MHC, Immuno Polymorphism Database-MHC; IFNa, interferon-alpha; IFNb, IFN-beta; IFNg, IFN-gamma; IL, interleukin; mAb, monoclonal antibodies; MHC, major histocompatibility complex; MIC, MHC class I chain-related genes; MLR, mixed lymphocyte reaction; Mo-DC, monocyte-derived DC; NK, natural killer; NIPC, plasmacytoid DC or natural interferon-producing cell; PCR-SSP, PCR-sequence-specific primers; PCR-RFLP, PCR-restriction fragment length polymorphism; PAM, pulmonary alveolar macrophage; PCV2, porcine circovirus type 2; PrV, pseudorabies virus; QTL, quantitative trait loci; SLA, swine leukocyte antigen; TAP, transporter-associated with antigen processing; TNF, tumor necrosis factor.

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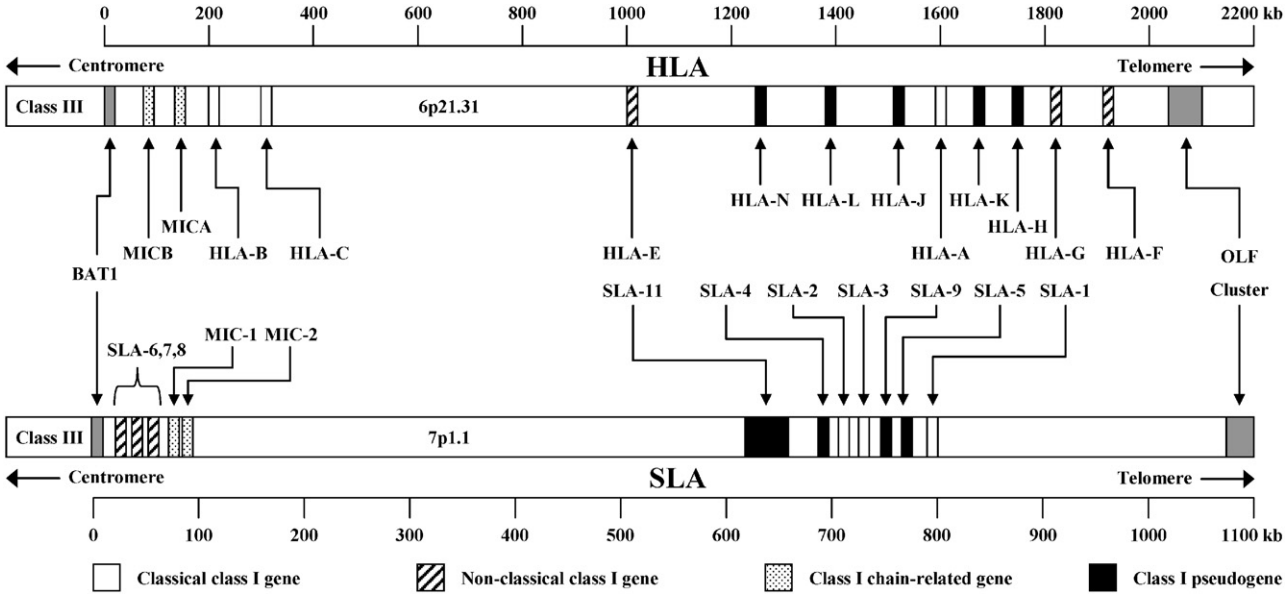

Fig. 1. Comparative genomic organization of the human and swine major histocompatibility complex (MHC) class I region. The human leukocyte antigen (HLA) class I map is adapted from Ref. [17] and the swine leukocyte antigen (SLA) class I map is based only on one fully sequenced haplotype (Hp-1.1, H01) [4]. Note that not all the genes are shown here and the scale is approximate. The number and location of expressed SLA class I genes may vary between haplotypes.

2.2. Mapping of the SLA class I region

There are seven classical class I genes and three non-classical class I genes mapped to the SLA complex (Fig. 1). From the most centromeric *SLA-11* locus in the classical class I gene cluster, the order of the genes is *SLA-4*, *SLA-2*, *SLA-3*, *SLA-9*, *SLA-5* and *SLA-1*. The constitutively expressed classical SLA class I genes are *SLA-1*, *SLA-2* and *SLA-3*, while the rest are pseudogenes. Increasing evidence also suggests that some SLA haplotypes have a duplicated *SLA-1* locus [16]. This duplicated locus was not identified in the Hp-1.1 haplotype; it has been tentatively designated *SLA-1′* until studies further characterize this locus. Although the *SLA-5* locus appears to have an intact coding region as do the functional class I genes, its promoter region harbors several mutations which may modify or eliminate its expression [8]. Further, no *SLA-5* clones were found in a swine cDNA library of spleen tissue screened with a MHC class I gene probe (Smith et al., unpublished data). The non-classical class I genes are *SLA-6*, *SLA-7* and *SLA-8*, and are located at the centromeric end of the class I region. Similar to the human leukocyte antigen (HLA) system, the SLA class I region also harbors the MHC class I chain-related genes (MIC). In swine only the *MIC-2* is predicted to be functional while the *MIC-1* gene appears to be a pseudogene. As shown in Fig. 1, the overall genomic organization of the SLA class I region is quite different from that of the HLA class I region.

Phylogenetic analyses showed that the SLA class I genes displayed much more sequence homology to each other than to the

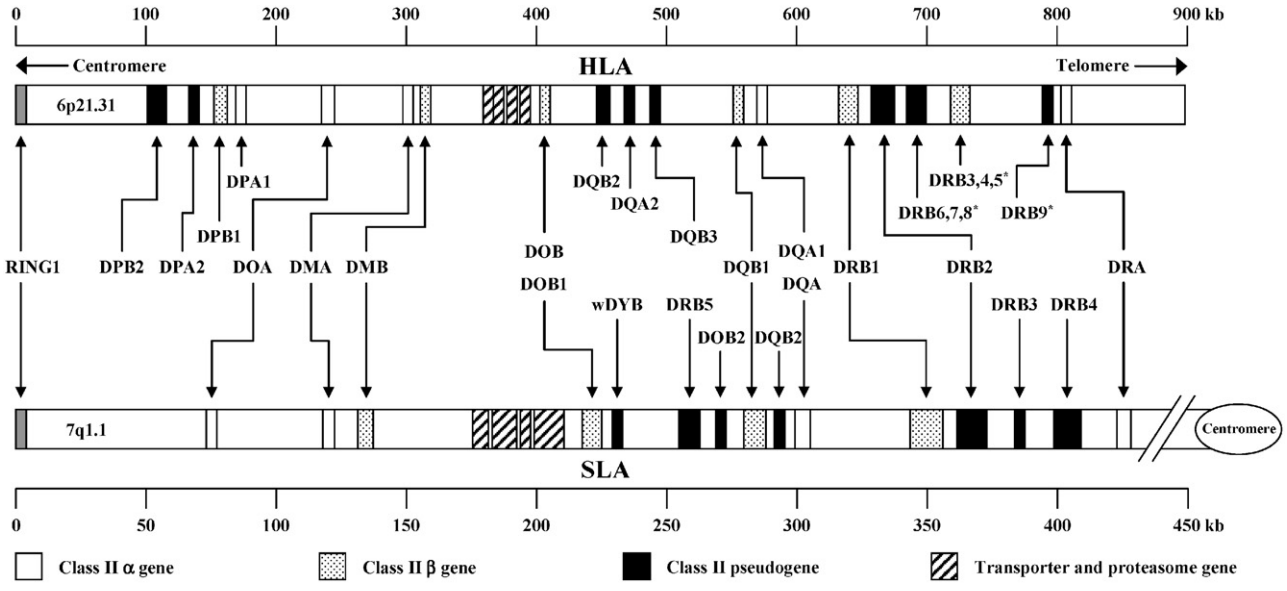

Fig. 2. Comparative genomic organization of the human and swine major histocompatibility complex (MHC) class II region. The human leukocyte antigen (HLA) class II map is adapted from Ref. [17] and the swine leukocyte antigen (SLA) class II map is based only on one fully sequenced haplotype (H01) [4]. Note that not all the genes are shown here and the scale is approximate. *The number and location of expressed *HLA-DRB* genes and pseudogenes may vary between haplotypes.

HLA class I genes [16]. As a result, the SLA class I genes were named with numbers to avoid the implications that any of these loci were more homologous to the *HLA-A*, *HLA-B* or *HLA-C* genes of the HLA system. Furthermore, sequence comparison indicated that the *SLA-1* and *SLA-3* genes are more similar to each other, as is the *SLA-1′*, than they are to *SLA-2*. Therefore, it is likely that these arose as gene duplications after speciation of pigs from humans. The *SLA-2* has a conserved but dichotomous sequence from codons 77–83, which is similar to the HLA-Bw4 and Bw6 sequences in the *HLA-B* alleles. In humans, the *HLA-B* and *HLA-C* loci are thought to have arisen from a gene duplication event after speciation. Thus, the differences in gene organization of the MHC class I region in mammalian species is probably due to gene duplications after speciation.

2.3. Mapping of the SLA class II region

There are several loci encoding the expressed SLA class II antigens; they include the α- and β-chain genes for the SLA-DR, -DQ, -DM and -DO proteins. From the most centromeric *SLA-DRA* gene in the class II gene cluster, the order of the expressed SLA genes is *DRB1*, *DQA*, *DQB1*, *DOB1*, *DMB*, *DMA* and *DOA* (Fig. 2). In contrast to the HLA system, there are no loci encoding the DP proteins. In addition, based on the only sequenced haplotype (Hp-1.1), there are several class II β-chain pseudogenes in the SLA class II region; their number likely varies between haplotypes, as observed in the HLA system [17,18]. The SLA class II pseudogenes include the *DRB2*, *DRB3*, *DRB4*, *DRB5*, *DQB2*, *DOB2* and *wDYB*. The *SLA-wDYB* gene (with the "w" to indicate tentative designation of this locus) is a two-exon fragment which appears to share similarity with the artiodactyl-specific *DYB* gene. Similar to the HLA class II system, genes that are involved in the antigen presentation pathway, such as the transporter-associated with antigen processing (TAP) genes (*TAP1* and *TAP2*) and proteasomes (*PSMB8* and *PSMB9*), are also located in the class II region between the *DOB1* and *DMB* loci. Taken together, the overall genomic organization between the SLA and HLA class II region is well conserved, except that the length of the SLA class II region is much shorter. Phylogenetic analyses also showed that the SLA class II genes demonstrated much stronger sequence homology with their HLA counterparts than they do with each other [19]. As a result, the functional SLA class II genes were named after their human counterparts to indicate the homology between the two systems.

2.4. Mapping of the SLA class III region

The SLA class III region is centromeric and physically linked to the contiguous class I region. Over 60 loci have been characterized in this region, including many important genes in the immune defense mechanism, such as the tumor necrosis factor (TNF) gene families (*TNF*, *LTA* and *LTB*), the steroid cytochrome P450 21-hydroxylase (*CYP21*) enzyme, and components of the complement cascade (*C2*, *C4A* and *CFB*) [4,20,21].

3. Function and structure of the SLA antigens

3.1. The SLA class I antigens

The functional classical SLA class I genes (*SLA-1*, *SLA-2* and *SLA-3*) code for 45 kDa transmembrane glycoproteins (consisting of three extracellular domains, α1, α2 and α3) that are non-covalently bound to 12 kDa β_2-microglobulin (b2m) has been mapped to chromosome 1 [22]. The α1 and α2 domains resemble each other in structure and together form the peptide-binding groove, whereas the α3 domain is a binding site for the CD8 co-receptor. These heterodimeric proteins are constitutively expressed on the surface of virtually all nucleated cells and function mainly in presenting peptides to CD8+ cytotoxic T cells. They also interact with natural killer (NK) cells to prevent NK-mediated cytotoxicity [23]. It has been suggested that the *SLA-1* gene has the highest expression level whereas the *SLA-3* has the lowest [24–26].

The exact functions of the non-classical SLA class I genes (*SLA-6*, *SLA-7* and *SLA-8*) have not been determined, but similar to the classical SLA class I genes they were also predicted to code for membrane-bound cell surface glycoproteins with the potential of binding peptides [7]. Their association with b2m is also not known. It is generally believed that they play some specialized roles similar to that of the non-classical HLA genes (*HLA-E*, *HLA-F* and *HLA-G*), yet searches in humans and mice for a gene homologous to *SLA-6* had proved negative [27]. Expressions of the *SLA-6* and *SLA-8* mRNA transcripts have been detected in a variety of tissues with very low levels in the brain. *SLA-7* mRNA transcripts exhibited more limited tissue distribution with high levels in thymus, and none detected in the kidney, brain and peripheral blood mononuclear cells [27,28]. Expression pattern results suggested that *SLA-6* is more similar to *HLA-E* than to *HLA-F* or *HLA-G*.

The function and structure of the swine MIC proteins remains to be determined. In humans, the *MIC* genes encode membrane-bound proteins which do not associate with b2m, do not present peptides, and have restricted tissue distribution (reviewed in Refs. [29,30]). The MIC proteins in humans are the ligands for the NKG2D receptor expressed by the NK cells, γδ T cells and CD8+ αβ T cells and thus are thought to serve as a marker for immune surveillance; their role in swine has not been determined.

3.2. The SLA class II antigens

The expressed SLA class II antigens (DR and DQ) are found primarily on the surface of professional antigen presenting cells (APCs), such as macrophages, B cells and dendritic cells (DCs) [31,32]. Their expression on various capillary endothelia in pigs has also been documented [21,33]. Unexpectedly, T cells express SLA class II antigens, with preferential expression on the CD8+ T cell subset [34–37]. Moreover, a minority of the circulating porcine CD2+CD8+ γδ T cells coexpress MHC class II [38]. SLA class II antigens function mainly in presenting exogenous peptides to CD4+ helper T cells. The SLA class II antigens are heterodimeric proteins which consist of an α chain of 34 kDa non-covalently bound to a β chain of 29 kDa. The α1 and β1 domains resemble each other in structure and together form the peptide-binding groove. In humans, the DM and DO are heterodimeric proteins which are involved in catalyzing and inhibiting the loading of antigenic peptides onto the DR and DQ proteins; their role in swine remains to be determined.

4. SLA gene structure

4.1. Genomic structure of the SLA class I genes

The genomic structure of the SLA genes is shown in Fig. 3. Classical SLA class I genes consist of eight exons: exon 1 encodes the leader sequence; exon 2–4 encode corresponding extracellular α1, α2 and α3 domains; exon 5 the transmembrane domain; and exon 6–8 the cytoplasmic domain [39]. All of the expressed classical class I genes have a high degree of similarity in the coding region. The *SLA-1* and *SLA-3* genes are also very similar in their untranslated regions, whereas the *SLA-*

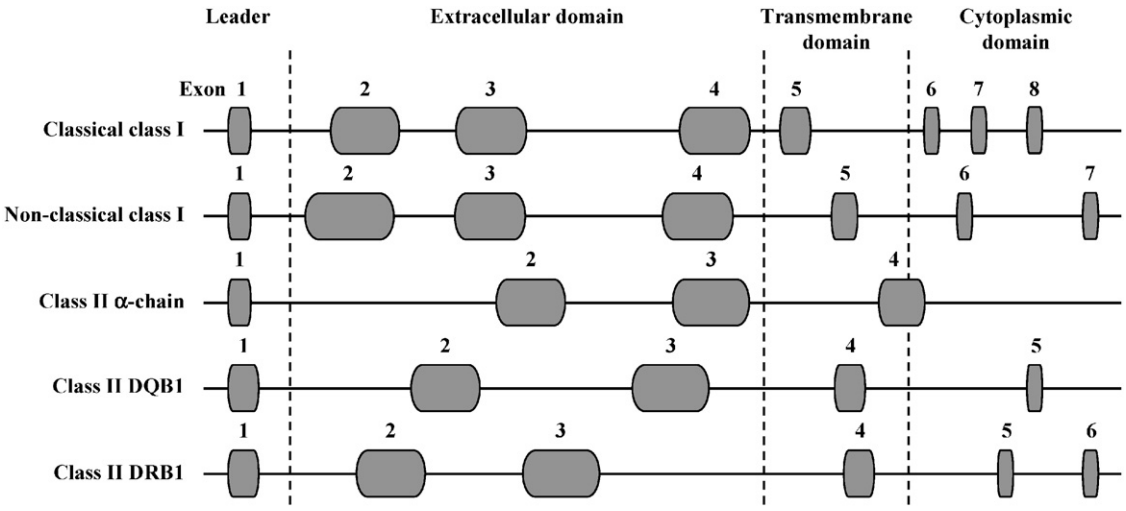

Fig. 3. Schematic molecular organization of the SLA genes. Exons are represented by the gray ovals and introns by lines. Gene length is approximate to that found for the Hp-1.1 genome sequence [4].

2 gene is 9-bp longer in the leader sequence. The non-classical SLA class I genes have similar molecular arrangements as the classical class I genes except only two exons encoding the cytoplasmic domain [27]. The *SLA-7* and *SLA-8* genes were found to have a greater resemblance in coding regions to each other than to the *SLA-6* gene [7]. The *SLA-8* gene is encoded in the opposite strand without an interferon regulatory element in its promoter region which suggested that this gene might be regulated differently than the *SLA-6* and *SLA-7* genes. Evidence also suggested that the *SLA-6* gene may undergo alternative splicing (Smith et al., unpublished data), similar to the non-classical *HLA-G* gene.

4.2. Genomic structure of the SLA class II genes

The class II *DRA* and *DQA* genes consist of four exons, with exon 1 encoding the leader sequence, exon 2 and 3 encoding the corresponding extracellular α1 and α2 domains, and exon 4 encoding both transmembrane and cytoplasmic domains (Fig. 3; [40,41]). The class II β-chain genes have essentially the same molecular structure as the α-chain genes except that the *DQB1* and *DRB1* genes have an additional one and two exons, respectively, encoding the cytoplasmic domain [42,43].

5. SLA nomenclature system

Due to the efforts of numerous investigators around the world, DNA sequences of many SLA genes and alleles have been determined and accumulated in several nucleotide sequence databases. The Nomenclature Committee for Factors of the SLA System was formed at the 2002 International Society for Animal Genetics conference in Göettingen, Germany to establish the principles of a systematic nomenclature system for SLA class I and class II genes and to assign alleles that have been defined by DNA sequencing [16,19]. The SLA Nomenclature Committee has established a publicly available SLA sequence database at the Immuno Polymorphism Database-MHC (IPD-MHC) website (http://www.ebi.ac.uk/ipd/mhc/sla/) to serve as a repository for maintaining a list of all recognized genes and their allelic sequences [16,19,44]. This provides investigators with a centralized platform to access the most recent information in the field of SLA research, such as the nomenclature reports, lists of SLA genes, alleles and haplotype assignments. It serves as a convenient site to submit both new and confirmatory allele sequences and their associated studies for the considerations of allele name assignments. A major update to the IPD-MHC SLA website was completed in May 2008 (Ho et al., in preparation). The IPD-MHC website has also added new sequence submission tools that allow continuous updating of new allele sequences.

5.1. The SLA alleles

The SLA nomenclature systems designated alleles of each locus into groups based on sequence similarity (identification of "group-specific" polymorphic sequence motifs) [3,16]. The allelic group assignments were based primarily on polymorphisms in the exon 2 and 3 sequences for class I alleles and exon 2 sequences for class II alleles, given that these regions encode the peptide-binding domains as well as interact directly with the immune cell receptors and are therefore considered to be functionally vital.

5.2. The SLA haplotypes

Given the strong linkage disequilibrium exhibited by the SLA loci, it is sometimes more appropriate and convenient for researchers to communicate and present findings in terms of haplotypes (a specific combination of alleles of genes on the same chromosome) rather than individual allele specificities [3,16]. The SLA Nomenclature Committee established a nomenclature system for SLA class I and II haplotypes that were defined by means of high resolution DNA sequencing (Tables 1 and 2). These high resolution SLA haplotypes are named with a prefix "Hp-", and a number for the class I haplotype followed by a number for the class II haplotype separated by a period (e.g. Hp-1.1). The number "0" is assigned if there was no information on the associated class I or class II haplotype (e.g. Hp-1.0). Further, a lower case letter is added to the haplotype numbers for the indication that they are closely related (e.g. Hp-1a.0 vs. Hp-1b.0); as of May 2008 there are 26 independent (28 total) class I and 20 (21) class II assigned haplotypes (Tables 1 and 2). Increasing evidence suggested that the number of expressed class I loci is haplotype-specific; phylogenetic and sequence analyses suggested that at least 9 class I haplotypes identified to date have the duplicated *SLA-1′* locus. Studies also have shown that haplotype Hp-2.0, Hp-3.0 and Hp-5.0 do not appear to express the SLA-3, SLA-1 and SLA-6 antigens, respectively [45,46].

Table 1
SLA class I haplotype assignment

Hp-[a]	Breed[b]	Previous designation	*SLA-1*	*SLA-3*	*SLA-2*	*SLA-6*
1a.0	Large White	H01	0101	0101	0101	0101
1b.0	Large White	H28	01rh28	01rh28	0101	ND[c]
2.0	NIH, Sinclair, Hanford	a, b, H10	0201, 0701	Null[d]	0201	w02sa01
3.0	NIH	c, H59	Null[d]	0301	0301	0103
4a.0	NIH, Duroc	d, H04	0401	0401	0401	0102
4b.0	Yucatan	x	0401	0401	040201	0104
4c.0	Meishan	K	0401	0401	0401	0104
5.0	Yucatan	w	0401	05sw01	w08sw01	Null[d]
6.0	Yucatan	y	08sy01	0601	05sy01	03sy01
7.0	Yucatan	z	0801	0701	0502	0101
8.0	Westran	None	02we02, 04we01	0302	07we01	01we01
9.0	Sinclair, Hanford	a	0601	0501	0601	ND
10.0	Sinclair	c	0501	hm22	0302	ND
11.0	Sinclair	d	0101, w09sm09	0701sm19	0501	ND
12.0	Hanford	e	08sm08, w09sm09	0502	10sm01	ND
13.0	Hanford	f	w10sm21	0401	w13sm20	ND
14.0	Large White	H12	0102	01rh12	07rh12	ND
15.0	Large White	H34	0102	07rh34	05rh34	ND
16.0	Clawn	c1	0401	0602	w09an02	ND
17.0	Clawn	c2	ND	03an02	06an03	ND
18.0	Meishan	M	0401	0304	06me01	0102
19.0	Meishan	N	08ms05, 13ms21	0602	w09sn01	0105
20.0	Meishan	L	w10cs01, cs02	0101	110102	0103
21.0	Commercial breeds	H03	rh03	0601	05rh03	ND
25.0	Hampshire[e]	None	1101	0302	0701	ND
27.0	Duroc	d1	06an04, 08an03	0101	0102	ND
56.0	Korean native pig	None	11jh01	0303	jh01	w04jh01
59.0	Korean native pig	None	11jh02	0503	jh02	0102
60.0	Duroc	d2	an02	0502	1002	ND

[a] SLA class I haplotype assignment based on Smith et al. [16].
[b] Breed in which the haplotype was sequence-based typed; haplotype may be found in other breeds.
[c] ND, not determined.
[d] Null, no expression of this locus.
[e] Haplotype was observed in the LLC-PK1 porcine cell line (ATCC) which was derived from a Hampshire pig.

Table 2
SLA class II haplotype assignment

Hp-[a]	Breed[b]	Previous designation	*DRA*	*DRB1*	*DQA*	*DQB1*
0.1	Large White, Korean native pig	H01	010101	0101	0101	0101
0.2	NIH, Sinclair, Hanford	a, b	010101	0201	0201	0201
0.3	NIH	c	0201	0301	0102	0301
0.4	NIH	d	010102	0201	020201	040101
0.5	Yucatan	x	020301	0501	020202	0201
0.6	Yucatan	w	020203	0501	0103	0801
0.7	Yucatan	y	0203my01	0601	01my01	0601
0.8	Yucatan	z	010101	0801	0203	0202
0.9	Westran	None	0101we01	0201	03we01	0402we01
0.10	Sinclair, Hanford	a	ND[c]	0401	ND	0801
0.11	Sinclair	c	020202	0901	ND	0402
0.12	Sinclair	d	020201	0602	0301	0701
0.13	Hanford	e	ND	0403	ND	0303
0.14	Meishan	M, K	010103	0901	0301	0801
0.15a	Meishan	N	0201	0401	0203	0201
0.15b	Banna	None	020301	0402	020202	0202
0.16	Clawn	c1	ND	11ac21	ND	0601
0.17	Clawn	c2	ND	0801	ND	0501
0.18	Meishan	L	010103	1401	02cs01	040102
0.25	Hampshire[d]	None	ND	1301	ND	0901
0.30	Korean native pig, Duroc	d1	020202	1101	02jh01	0503

[a] SLA class II haplotype assignment based on Smith et al. [19].
[b] Breed in which the haplotype was sequence-based typed; haplotype may be found in other breeds.
[c] ND, not determined.
[d] Haplotype was observed in the LLC-PK1 porcine cell line (ATCC) which was derived from a Hampshire pig.

6. SLA gene polymorphism and typing methods

One of the most remarkable features of the MHC genes is the extremely high degree of genetic polymorphism within loci. The MHC Haplotype Project affirmed that they are the most polymorphic genes in the vertebrate genomes with 300 total loci, including 122 gene loci with coding substitutions of which 97 were non-synonymous [18]. In the HLA system, over 2000 class I alleles and 900 class II alleles have been identified to date [47]. This extreme polymorphism is believed to have arisen in response to

the evolutionary pressures generated by encounters with pathogens [48]. The unique peptide-binding motif of each MHC allele will affect the range of peptides that can be bound.

6.1. Polymorphism of the SLA class I alleles

Based on the IPD-MHC SLA database a total of 116 SLA classical class I alleles and 13 non-classical class I alleles have been identified to date. The *SLA-1*, *SLA-3* and *SLA-2* genes are highly polymorphic [3]. There are 12 *SLA-1* allele groups with a total of 44 alleles; 7 *SLA-3* allele groups with 26 alleles, and 14 *SLA-2* allele groups with 46 alleles. The extreme polymorphisms of the SLA class I genes are, as expected, concentrated in exons 2 and 3 of the coding regions which form the class I protein peptide-binding groove. Sequence length variations have been observed in several SLA class I alleles (Ho et al., in preparation). It is yet not known whether these sequence length variations would affect the structural integrity of the proteins and thus modify their surface expressions.

The non-classical *SLA-6* gene appears to be largely monomorphic. There are only 9 *SLA-6* alleles representing 4 allele groups reported to date with very minor nucleotide substitutions between alleles. There are only 2 alleles that have been reported for the *SLA-7* and *SLA-8* genes [7,28]; the 2 *SLA-7* alleles differ by 8 nucleotide positions while the 2 *SLA-8* alleles differ at 7 positions.

6.2. Polymorphism of the SLA class II alleles

There are a total of 167 SLA class II alleles identified to date (128 β-chain; 39 α-chain alleles) with polymorphisms mainly located in exon 2 of the coding sequences [16]. The *SLA-DRB1* and *-DQB1* loci display a very high degree of polymorphism. There are 14 *DRB1* allele groups and a total of 82 alleles; and 9 *DQB1* allele groups with 44 alleles. The *SLA-DQA* locus exhibits a moderate degree of polymorphism with 20 alleles identified to date. As with *HLA-DRA*, the *SLA-DRA* locus exhibits a very limited polymorphism with 13 alleles representing 3 allele groups, despite the fact that it also encodes part of the domain for binding antigenic peptides. Ando et al. [49] characterized the DNA sequence of five *SLA-DMA* alleles which showed only a few nucleotide substitutions in exon 3 and exon 4 of their coding regions. As with the SLA class I system, a few sequence length variants have been detected in SLA class II genes (Ho et al., in preparation). It is unknown whether these variations will affect the structural integrity of the proteins or modify their surface expressions.

6.3. SLA typing by serology and mixed lymphocyte culture

Due to the extensive polymorphic nature of SLA genes, accurate typing methods are crucial for studying SLA effects in production traits and disease resistance. Historically, serologic typing methods using alloantisera have been the most important means for determining SLA class I antigen specificities [50]. This method is fast, simple and inexpensive to perform. However, there is limited availability of typing sera with well-defined specificities, typing sera are not available for many alleles, and SLA typing sera developed in France are not readily available in the United States because of the strict import regulations. Moreover, MHC molecules often share similar epitopes that can be bound by the same antibody which makes most SLA typing sera highly cross reactive. Most of these typing reagents are directed against an entire haplotype rather than individual allele specificities which make the resolution undesirable. Such reagents have been useful for SLA inbred pigs such as the NIH SLA-defined minipigs; because of recombinant SLA haplotypes in these pigs class I and class II alloantisera have been produced [52]. Serologic typing also has inherent limitations on its ability to distinguish between alleles that differ at sites that are inaccessible to antibody binding (e.g. epitopes that are buried within the SLA proteins). Few antisera capable of identifying all SLA alleles have been made, although monoclonal antibodies (mAb) with broad SLA class I or II specificity are available [11,53]. The lack of typing sera creates problems since many animals often have untyped or "blank" SLA antigens.

The mixed lymphocyte reaction (MLR) has historically been the most important method for defining SLA class II antigen specificities [54]. The MLR results from T-cells proliferating to class II antigen incompatibilities present on the stimulating cells [55,56], whereas class I antigen mismatches alone only lead to slight proliferative responses [57]. Nevertheless, MLRs are labor intensive, technically demanding and very time consuming to perform. MLRs require reference lymphocytes with defined SLA specificities, thus, typing random outbred pigs is not practical and would require an enormous bank of reference cells. Only with closed herds of pigs with limited and defined SLA specificities has the MLR typing method proved reasonably effective [51,58].

6.4. SLA typing by molecular methods

A variety of molecular based methods have been described for typing SLA alleles. Sequence-based typing, DNA sequencing of SLA alleles, is the most direct and accurate method [46,59,60]. However, this approach usually requires cloning of the alleles to resolve heterozygous sequences. It is labor intensive, technically demanding, time consuming and cost-prohibitive to be implemented on a large scale, e.g. in outbred pig herds. Sequence-based typing is most suitable for characterizing the SLA types of parental or founder breeding animals of pedigreed pig populations. This can then be followed with other more cost effective methods for SLA typing of the offspring, using PCR-sequence-specific primers (PCR-SSP), PCR-restriction fragment length polymorphism (PCR-RFLP) or microsatellite (MS) markers.

PCR-SSP has been described for typing SLA alleles in several inbred herds of pigs [60–63]. This method of typing is based on the fact that primer mismatch to the alleles, especially at the 3′-end of the primers, interferes with the polymerase extension during PCR. Only reactions with the primers that are completely matched to the SLA alleles will have successful amplifications with DNA prepared from the test pig cells and produce products. This method of typing is fast, accurate and inexpensive to perform. However, it is limited to alleles with previously known DNA sequences to which sequence-specific primers can be designed.

PCR-RFLP analysis has been described to examine the SLA allelic differences [60,63]. This method of typing is generally fast, easy and relatively inexpensive to perform. However, the resolution greatly depends on the availability of restriction enzymes for differentiating specific polymorphic sites. As the number of polymorphisms assayed increases, the expected reaction patterns can quickly become complicated and difficult to interpret.

Haplotyping using MS markers within the MHC region has also been described as a surrogate test for SLA loci [64–66]. The MS typing method is fast, easy, inexpensive to perform, and has been implemented widely for genetic mapping of quantitative trait loci (QTL) that affect production traits [67]. However, the resolution of this method greatly depends on the availability and comprehensiveness of the markers in the region; recent thorough MS mapping results have identified recombination events within the SLA complex to a much finer location [66]. Further, the heterogeneity of the markers does not necessarily correlate with the SLA haplotypes. In summary, SLA typing of

pedigreed populations can be greatly facilitated with MS typing, whereas typing of unpedigreed outbred pigs is likely to give ambiguous results.

7. SLA diversity, recombination within the SLA region

With numerous swine breeds worldwide, the extent of SLA diversity in outbred pig populations is still not known. At least 72 serologically defined SLA class I haplotypes (designated H01–H72) have been reported [15,50]; the majority of these haplotypes reflected European commercial pig breeds and not represent the SLA diversity in other pig populations. To date, a total of 29 SLA class I haplotypes and 21 SLA class II haplotypes have been defined by means of high resolution DNA sequencing (Tables 1 and 2). Moreover, the haplotypes found in the SLA-defined NIH miniature pig lines, established by Sachs in the USA [51], resembled known haplotypes [SLA^a as H10, now Hp-2.2; SLA^d H04, now Hp-4a.4; however, SLA^c did not correlate with any previously identified serologic haplotype and was designated H59, now Hp-3.3].

With PCR-SSP SLA typing methods to date we have identified a total of 49 class I and 30 class II SLA haplotypes after testing nearly 850 pigs obtained from multiple commercial sources (Ho et al., in preparation). Altogether, these numbers corresponded to merely 5.5% and 3.4%, respectively, of the maximum number of predicted SLA class I and II haplotypes. Thirty-three of the class I, and 15 of class II, haplotypes appeared to be novel and did not have high resolution DNA sequenced counterparts. This suggests that there is a low SLA diversity in commercial pigs due in part to selection and resultant inbreeding required for maintenance of desirable production traits in modern pig production.

There are few studies that have documented recombination events in the SLA region. Based on earlier data there is substantial linkage disequilibrium; the overall recombination frequencies were reported to be 0.4–1.2% within the SLA region and 0.05% within the class I region [3,15,52,54,68,69]. Crossover within the SLA class II region has not yet been reported. This recombination frequency may be an underestimate due to the detection limits of older serologic and cell-based typing methods. Most previously documented crossovers mapped to the SLA class III region, suggesting a recombination hotspot. However, recently 3 recombinants within the SLA class I region, and 3 between the class I and class II region, were identified using PCR-SSP in the Sinclair and Hanford miniature pig crosses established for swine melanoma research. These corresponded to crossover frequencies of 0.56% between the class I and class II region and 0.39% within the class I region [67] (Ho et al., in preparation). The higher crossover frequency (0.39%) within the class I region may be due to better detection methods and/or the presence of recombination hotspots in certain haplotypes. An additional 3 SLA class I recombinants were detected in Clawn miniature pigs using MS markers [66].

One of the class I recombinants detected in the Sinclair and Hanford miniature pig crosses appeared to have occurred between the *SLA-1* and the duplicated *SLA-1′* loci of haplotype Hp-2.0 and Hp-11.0. This particular crossover, for the first time, allowed the spatial assignment of the *SLA-1**0201 and *SLA-1**w09sm09 alleles to the centromeric *SLA-1* locus and the *SLA-1**0701 and *SLA-1**0101 alleles to the telomeric *SLA-1′* locus in their respective haplotypes (Ho et al., in preparation).

8. SLA gene regulation of swine disease responses

8.1. Introduction: HLA and immunity; swine models

Past research has identified the influence of the human MHC, or the HLA genes, in determining transplantation success for most organs and tissues [70–75]. The swine model has been an important contributor to that knowledge particularly the work using SLA-defined pigs for allo- and xeno-transplantation studies [76–79]. Studies demonstrated that human CD4+ T cells responded to porcine islets xenoantigens by the indirect antigen pathway presentation; the major porcine xenoantigens recognized are SLA class I molecules [80,81]. Transplantation among SLA-identical pigs has proven to be a useful model to assess the relative in vivo roles of bone marrow from normal and von Willebrand factor defective pigs in hemostasis and thrombosis [82].

The role of HLA genes in cancer and infectious disease responses has been informed by the expanded understanding of expression of both classical and non-classical class I molecules, HLA-G, CD1a, and their interaction with NK cell targets, the killer cell immunoglobulin-like receptors [83–87]. Early mapping studies in the Sinclair spontaneous swine melanoma model determined that a single dose of a specific SLA haplotype was required for tumor initiation [58,88–90]. More detailed QTL studies using the Melanoma-bearing Libechov Minipig model identified numerous melanoma candidate loci with highly significant QTLs on several chromosomes for precise disease traits [91,92].

A role for HLA genes as important risk factors for autoimmunity, e.g. the association of HLA-B27 with ankylosing spondylitis, is well established. HLA class II alleles determine risk of autoimmunity, e.g. for diabetes susceptibility, both susceptible and protective HLA-DR and -DQ polymorphisms are known to bind and present non-overlapping antigenic peptides [93,94]. Swine are excellent models for immune system development [95], as well as good models for food allergies and liposome and other lipid-based nanoparticles hypersensitivity reactions [96,97].

The last decade has seen major progress in the understanding of the requirement for MHC processing of foreign antigens for human immune, vaccine and infectious disease responses. Studies have defined the exact peptide epitopes presented by many class I or II antigens that stimulate protective anti-pathogen responses; this has revolutionized the means for identifying vaccine epitopes and viral persistence targets [98–106]. Many infections modulate HLA expression, e.g. HLA class I is down-regulated by human immunodeficiency virus (HIV) infection [107]. HLA imprints HIV replication and in the process alters host responses; cytotoxic T cell HIV escape variant viruses when transmitted to HLA class I mismatched recipients are associated with lower viral loads and higher CD4+ counts thus potentially attenuating the virus [108,109].

8.2. SLA expression on immune cell subsets

Studies in numerous species have proven that the level of MHC expression is a major factor in determining activity of APC, including macrophages and DC. As expected from other species, swine B cells and macrophages express both SLA-DR and -DQ antigens [31,110,111]. Putative B-cell precursors express high levels of SLA-DR and low levels of CD2 and CD25 [112]. Unexpectedly, T cells express higher levels of SLA-DR than -DQ antigens; moreover, there is preferential expression of class II antigens on CD8+ T cell subsets; CD4−CD8+ and CD4+CD8+ T cells subsets do express SLA class II [34–37]. The importance/relevance of this unusual class II T cell expression has yet to be fully explained. Moreover, a minority of the circulating porcine CD2+CD8+ γδ T cells coexpress MHC class II and some surface markers normally associated with APC, e.g. CD80/86, CD40 and CD31, but not CD14 or CD172a [38]. Class II MHC antigens are expressed on porcine intestinal and renal vascular endothelium [33,113]. Normal pig endothelial cells express SLA class I and up-regulate class II in response to IFNg; those immortalized by the

introduction of SV40 T antigen, retain these original characteristics [114–116].

Porcine bone marrow progenitor cells, identified by the anti-c-kit mAb, have low levels of SLA class II [117]. SLA class II was only detectable on osteogenic differentiated mesenchymal stem cells whereas SLA I was found on both differentiated and undifferentiated cells and neither stimulated MLRs with human cells [118]. Adult mesenchymal stem cells are SLA I+ but SLA II− when isolated from bone marrow using aptamers [119].

Summerfield et al. [32] delineated porcine blood APC subsets, the blood monocytes that are SLA class II+, CD14+ and the blood DC which are SLA class II+ but CD4−CD14−. Plasmacytoid DCs, equivalent to the natural interferon-producing cells (NIPCs), are strong interferon (IFN) type I secretors after virus stimulation and are typically CD4++, MHC class II low. Both DC subsets are endocytically active when freshly isolated, and down-regulate this activity after in vitro maturation. When monocytes are split into CD163+ and CD163− cells, both subsets give rise to DC. However, compared to CD163− monocyte-derived DC (MoDC), CD163+ MoDC appear to have reached a more advanced stage of maturation, expressing higher levels of SLA II and CD80/86 and more efficiently inducing proliferation of T cells to recall antigens and alloantigens [120]. Interestingly CD163+ is a marker for cells which are susceptible to both African swine fever virus (ASFV) and PRRSV infections [121,122].

Porcine monocytes and MoDCs respond to microbial pathogen-associated molecular patterns by altering toll-like receptor expression, up-regulating MHC II and CD80/86 and altering cytokine expression [123]. Porcine alveolar macrophages (PAMs) are poor accessory cells when compared with peripheral blood monocytes despite expression of SLA-DR antigens and other co-stimulatory adhesion molecules; they secrete relatively little interleukin-1beta (IL-1b), whereas blood monocytes were potent IL-1b secretors. Thus, PAMs may be important immunoregulatory cells with cytokine suppressor activity [124].

In mucosal sites different DC subsets have been identified. In small intestinal lamina propria at least two major populations of cells exhibit differential antigen presentation; the DC (CD45+ SLA class II+) are phagocytic and potent initiators of a primary immune responses whereas CD45− endothelial cells, despite significant amounts of MHC class II, do not trigger an MLR [125]. MHC class II molecule expression by gut-associated IFNa-producing cells was the first indications that these cells were the in vivo mucosal counterparts of DCs [126]. DC migration to mesenteric lymph nodes largely originates from the lamina propria; these lymph DCs express high levels of SLA class II and co-stimulatory molecules but have a low phagocytic capacity, indicating a mature phenotype, and did not induce MLR proliferation [127]. Moreover, their migration was not significantly influenced by mucosal antigen application. Cholera toxin promotes the development of a semi-mature DC phenotype, with lower expression of MHC class II and CD40, but increased CD80/86. Once primed with Cholera toxin DC were not actively tolerogenic and could not suppress proliferative T cell reactions induced by untreated DC [128].

8.3. SLA alleles and swine production and immune traits

Several authors have reviewed the potential of using genetic approaches to improve animal disease resistance [129–135]. Mallard, Wilkie and their colleagues have performed a series of experiments to establish populations of pigs that they predict will be more immunologically active and thus more resistant to infectious diseases; however, the high immune response pigs were more susceptible to *Mycoplasma hyorhinis* infection [136–138]. Edfors-Lilja et al. [139] traced QTL regulating normal immune traits. Several QTL influencing traits including growth, back fat thickness and carcass composition map to the SLA complex [67,140–143]. A QTL for fat androstenone levels in pigs maps to the SLA region but apparently not to the CYP21 or CYP11A loci [144]. One multivariate QTL detection analysis on fatness and carcass composition traits mapped QTL to at least four swine chromosomes, preferentially affecting one or the other group, but the SLA region always influenced all the traits [145]. Recent crosses indicate that it might be possible to apply a marker-assisted selection strategy, while controlling SLA allele diversity, to separate some of these QTL on chromosome 7 from the SLA loci [146].

As management changes in the pig industry alter the range of pathogens to which pigs are exposed, and as consumers demand pork products free of antibiotic contamination, it becomes increasingly more important that disease resistant breeding stock be available. Disease resistant pigs, in well-managed facilities, will help decrease drug usage by producers and increase the health of the nation's food supply. Several groups have attempted to evaluate the relationship between the level and function of circulating immune cells with average daily gain, live and carcass measurements, feed intake, and feed conversion [130–133]. One study showed that the CD16+, CD2+/CD16+, CD8+, and SLA-DQ+/− cell subsets appear to be important biomarkers involved with the inherent ability of the pig to efficiently grow and produce better carcass weight in representative commercial environments [147]. Overall these results could help guide breeders in selectively increasing the frequency of certain SLA alleles, i.e., those which are known to be associated with enhanced disease resistance or QTL effects.

Studies of the impact of genetic polymorphisms have clearly identified the SLA genes as the most important determinants of immune, infectious disease and vaccine responses by their specificity in binding and presenting foreign antigens as discussed in numerous reviews in this special issue. The influence of SLA encoded genes on immune and disease traits is broad. Based on studies using SLA-defined and SLA inbred lines of pigs it was affirmed that SLA genes determined levels of antibody responses to defined protein and vaccine antigens (Table 3). Similarly, cellular responses to defined antigens showed weak associations with specific SLA haplotypes. Earlier in vitro studies of SLA control of anti-bacterial responses [152–155] need to be confirmed *in vivo* by actual pathogen challenges. Because of the difficulty and expense of performing controlled disease challenge studies only limited numbers of such studies have been performed [13]. Lunney and colleagues have established that both primary and secondary responses to the foodborne helminth parasite *Trichinella spiralis* are regulated by SLA associated genes whereas no such SLA association was found for *Toxoplasma gondii* infections [153,158–161].

The tremendous expansion of our understanding of the complexity of MHC controlled responses and of techniques to assign SLA haplotypes and alleles over the last decade enabled researchers to expand their studies to assess the effects of specific SLA alleles on QTL and disease responses and to identify exactly which genes enable pigs to resist infection by specific pathogens. For PRRSV the 165 pig "Big Pig" study of viral clearance and persistence have resulted in a dataset for which SLA associations can be tested (Molina et al., unpublished data). However, the high diversity of SLA class I and II haplotypes, and complexity of anti-viral responses, in the 109 infected commercial pigs has resulted in no statistical associations of any anti-viral response trait with SLA haplotype (Wysocki et al., unpublished data).

Table 3
SLA gene encoded disease and vaccine responses

Immune parameter	Breed	SLA association	Reference
Antibody response levels			
Anti-lysozyme	Large White	Higher Hp-14.0; lower Hp-2.0	[148]
	NIH minipigs	Higher Hp-3.3; lower Hp-4a.4	[52]
Anti-model antigen	NIH minipigs	Higher Hp-4a.4	[52,149]
		Lower Hp-3.3	[52]
Anti-sheep red blood cell	NIH minipigs	Higher Hp-4a.4	[136]
Vaccination for *Bordetella bronchiseptica*	Various commercial breeds	Higher Hp-2.0	[150,151]
Cellular responses			
Salmonella bacterial phagocytosis	NIH minipigs	Higher Hp-2.2	[152]
Delayed contact type hypersensitivity induced by tuberculin protein	NIH minipigs	Higher Hp-4a.4	[138]
Parasite antigen proliferation	NIH minipigs	Higher Hp-3.3	[153]
Interferon induction	NIH minipigs	None significant	[154]
Bacterial phagocytosis	NIH minipigs	Lower Hp-2.2	[155]
Macrophage superoxide production	Inbred Yorkshire pigs	None with class II	[156]
Disease responses			
Melanoma initiation; tumor incidence	Sinclair model	Higher Hp-2.2	[58,88–90]
	Libechov Minipig model	QTL map to SLA	[91,92,157]
Response to primary *Trichinella* infection	NIH minipigs	Lower parasite burden in Hp-3.3	[153]
Response to secondary *Trichinella* infection	NIH minipigs	Faster anti-parasite in Hp-2.2	[158,159]
Response to primary *Toxoplasma* infection	NIH minipigs	None significant	[160]

8.4. Pathogen effects on SLA gene expression and regulation of swine immune responses

In vitro studies can reveal important details of pathogen responses. The clear evidence that SLA antigens are modulated during viral disease responses, e.g. to African swine fever viral, is just one indication of the role of these molecules in controlling infectious diseases [162,163]. In contrast, classical swine fever virus (CSFV) infection of porcine aortic endothelial cell caused no change in SLA-II, adhesion or co-stimulatory molecules, yet there was increased expression of mRNA for IL-1a and IL-6 [164]. Cytopathogenic CSFV induced a higher degree of DC maturation, in terms of CD80/86 and MHC II expression; the capacity of CSFV to replicate in myeloid DC, and prevent IFNa/b induction and DC maturation, requires both regulated viral double-stranded RNA levels and the presence of viral Npro [165]. Viral interactions with DCs have important consequences for immune defense function. The expression of MHC II and CD80/86 on the surface of DCs treated with porcine circovirus type 2 (PCV2) was not modulated nor did PCV2 induce DC maturation, in terms of MHC II and CD80/86 expression [166]. Yet virus persists within myeloid DCs in the absence of virus replication. Moreover PCV2-induced inhibition of the IFNa and TNF normally produced with CpG-ODN, thus disrupting NIPC function [166]. Skin DCs exhibit no change in SLA expression after infection by foot-and-mouth disease virus (FMDV), they express and store IFNa in uninfected animals and excrete IFNa in response to viral infection, thus conferring viral resistance [167]. Bacterial lipoprotein OprI from *Pseudomonas aeruginosa* has immunostimulatory properties for porcine DC, and has potential as vaccine immunostimulant for CSFV [168]. OprI-based expression vectors are valuable tools to screen ASFV antigens in terms of their capacity to trigger immune competent cells [169].

Pigs immunized with *Actinobacillus pleuropneumoniae* bacterins, that do not induce protection, when compared to pigs infected with low aerosol doses of *A. pleuropneumoniae*, which induces complete protection, indicated variation in cellular expression of SLA-DR and DQ but only changes in CD4:CD8 T cell ratios appeared relevant to protection [170]. Pigs are considered an important source of *T. gondii* infection for humans; early events in infection, e.g. increased expression of activation markers CD25 and SLA-DQ were associated with vigorous immune responses to the parasite [171].

Newer transcriptomic approaches are already revealing important host pathogen interactions. Based on microarray analyses of whole tissues early effects of *Salmonella* infection have revealed regulatory pathways controlling immune responses [172,173]. Recent microarray studies have demonstrated differential expression of genes associated with antigen presentation (pan SLA class I, *B2M*, *TAP1* and *TAPBP*) during microbiota induced immune responses and revealed distinct regulatory mechanisms common for these genes [174]. The availability of SLA and pseudorabies virus (PrV) viral arrays, and swine long oligo arrays, have enabled simultaneous analysis of viral and host gene expression and shown that several genes involved in the SLA class I antigenic presentation pathway (SLA-Ia, *TAP1*, *TAP2*, *PSMB8* and *PSMB9*) were down-regulated with PrV infection, thus contributing to viral immune escape from class I immune pathways [175]. These studies also identified genes involved in apoptosis and IFN-mediated antiviral responses and provided a global picture of transcription with a direct temporal link between viral and host gene expression.

Kinetic analyses of immune cell populations from piglets surviving in utero infection with PRRSV indicated modulation of cell numbers; CD2+, CD4+8+ and SLA-class II+ cells in peripheral blood, and CD2+ and CD3+ cells in bronchoalveolar fluid, were increased in piglets that were PRRSV infected in utero compared to the uninfected controls [176]. PRRSV exhibits productive replication in MoDC; resulting in reduced expression of SLA class I, class II, CD14 and CD11b/c and impaired MLR but no apparent change in the levels of IL-10, IL-12 and IFNg [177]. Thus, PRRSV productively infects MoDC and impairs the normal antigen presentation ability by inducing minimal Th1 cytokines.

8.5. Molecular analyses of T-cell antigen epitopes bound by SLA genes

Several studies have been aimed at identifying viral T-cell epitopes. FMDV synthetic pentadecapeptides which stimulated class-II restricted T helper cells proliferation and IFNg ELISPOTs were identified using cells from Hp-3.3 and 4a.4 minipigs and shown to represent class II and class I-restricted helper and cytolytic T cell epitopes [178]. Unfortunately no common epitope was found, but there was one overlapping peptide, thus providing information useful for the design of novel vaccines against FMDV [178]. Porcine endogenous retroviruses (PERV)-derived peptides both natural, or derived by purification from solubilized class I

molecules or from computer prediction, were efficiently presented on porcine and human MHC class I molecules. This data revealed CD8+ CTL responses elicited against dominant SLA and HLA class I-restricted PERV-derived epitopes may play an important role in xenograft rejection and in containment of PERV infection of human cells after xenotransplantation [179].

Oleksiewicz et al. [180] cloned the extracellular domains of SLA-I and linked them to b2m for two common Danish haplotypes (Hp-4.0 and H07). The engineered single-chain proteins were linked to peptides representing T-cell epitopes from CSFV and FMDV and tested in an in vitro refolding assay to potentially discriminate between peptide-free and peptide-occupied forms of SLA-I. Based on results with a proven CSFV epitope the in vitro refolding assay appeared able to discriminate between peptide-free and peptide-occupied forms of SLA-I [180]. Gao et al. [181] cloned the swine *SLA-2* gene and linked it to the b2m gene; the resultant fusion protein was expressed and purified; the refolded SLA-2-(G4S)3-b2m protein was used to bind three nonameric peptides derived from FMDV O subtype VP1. Results demonstrated that the reconstructed SLA-2-(G4S)3-b2m protein complex could be used to identify nonameric peptides, including T-cell epitopes in swine.

9. Conclusions

The last decade has seen major progress in swine immunology and genetics and particularly in understanding the SLA complex, its genetic loci and the role of SLA in normal immunity and in infectious disease and vaccine responses. The stage is now set for deeper probing of the role of SLA alleles and haplotypes in controlling these responses, for determining specific antigenic epitopes that stimulate immune and vaccine responses, and for identifying critical immune cell subsets and the exact SLA loci that facilitate cellular interactions for effective immune responses. Research using improved swine genome sequence and updated genomic and proteomic tools will reveal novel immune pathways regulated by SLA genes. In summary, the stage is now set for determining the critical role of SLA genes and proteins in swine biomedical models and in overall pig health and productivity.

Acknowledgements

There is a vast literature on the MHC, SLA and HLA complex structure, methods to assess alleles and their effects on immune responses. Due to limitations of citations we have included only the most recent publications.

Note: Based on the International Society for Animal Genetics guidelines all gene locus symbols are based on the Human Genome Organisation Gene Nomenclature Committee, http://www.genenames.org.

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